REMARKS

I. Status of the Claims

With entry of this amendment, claims 1 and 3 are pending in this application. Claims 1 and 3 are rejected. Claim 2 is canceled. Claims 4-12 are withdrawn. Claim 13 is new.

Solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, claim 1 is amended to more particularly describe the subject matter of the invention. Support for "[a] composition in combination with pharmaceutically acceptable diluents" of claim 1 may be found, for example, in the claims-as-filed and in the specification at page 3, lines 12-15. Claim 1 was further amended solely to conform to the restriction requirement presented in the Office communication of September 7, 2005, as clarified by the April 28, 2006, Office Action. *See* Office Action, page 2. This amendment should not be construed to disclaim or prejudice the subject matter of claim 1 as-filed.

Solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, claim 3 is amended to more particularly describe the subject matter of the invention. Support for "[t]he composition of claim 1, wherein the activator for plasma coagulation factor is selected from factor VII activating protease, the proenzyme of factor VII activating protease, factor XII, kinogen, and prekallikrein" of claim 3 may be found, for example, in the claims-as-filed and in the specification at page 3, lines 17-19.

Applicants add claim 13 to more particularly describe the subject matter of the invention. Support for "[t]he composition of claim 3, wherein the activator for plasma coagulation factor is selected from factor VII activating protease and the proenzyme of factor VII activating protease" of claim 13 may be found, for example, in the claims-as-filed and in the specification at page 3, lines 17-18.

III. The Claims Are Supported by the Specification

The Examiner maintains the rejection of claims 1 and 3 under 35 U.S.C. § 112, first paragraph, alleging that the specification "does not reasonably provide enablement for the treatment of a disease or disorder associated with coagulation via the administration of a pharmaceutical composition *in vivo*." Office Action, page 2. According to the Examiner, "the language 'pharmaceutical preparation' in the preamble of claims 1 and 3 implies a therapeutic or treatment benefit that is not enabled because the instant specification, nor the art, has shown a pharmaceutical benefit." Further, the Examiner alleges that "the specification is not enabled because the instant specification, nor the art, has not taught how a PNA would enhance coagulation, as instantly recited." *Id.* at 3.

Applicants respectfully traverse. The specification teaches a pharmaceutical preparation comprising either RNAs or PNAs to promote coagulation. The examples clearly illustrate the use of RNA to promote coagulation in plasma. PNAs are structurally similar to DNA and RNA with the exception of the neutral backbone. Numerous examples in the art show that PNAs function similar to RNAs. *See*, for example, Braasch et al. (Biochemistry, Vol. 41, No.14, 2002, p. 4503-10) ("Braasch").

Moreover, one skilled in the art would recognize that they could easily use PNAs to promote coagulation by following the steps outlined for RNA in the examples. Little experimentation would be required to demonstrate this effect.

The Examiner further asserts that "[s]ince peptide-nucleic acids are known to target and inhibit RNA with increased specificity, the specification has not taught how one could predictably promote coagulation by administering a pharmaceutical composition comprising a peptide-nucleic acid." Office Action, page 4. However, the inhibition of RNA by PNAs is not non-specific. PNAs with a particular base sequence can inhibit the RNA with the complementary sequence. Thus, PNAs do not have a general inhibitory effect on RNA. Moreover, in an extracellular context, the likelihood of having some native RNA that performs some coagulation function that happens to have a complementary sequence to the PNA applied is extremely remote. In fact, the specification describes a synthetic RNA comprised of poly IC, which would not encode the message for any protein in the cell and thus, is even more unlikely to be found in a natural form outside the cell. The poly IC synthetic RNA was highly effective for promoting coagulation. Specification, page 9, lines 12-15. Furthermore, one skilled in the art would recognize that if one were to add more than one type of PNA or RNA together to the outside of the cell, they would not add molecules with complementary sequences.

In addition, based on the Examiner's conclusion, PNAs behave no differently than RNAs. RNA also has both an inhibitory property towards other RNA and the ability to stimulate coagulation. In fact, PNAs are used for the very reason that they can

simulate the function of RNA when used for antisense applications inside the cell. Thus, one skilled in the art would predict that these PNAs would act in a similar fashion to RNA in the stimulation of coagulation when applied to the exterior of the cell.

Further, the skilled artisan would be able to utilize what is taught in the instant application along with the techniques known in the art to apply the pharmaceutical preparation containing RNAs or PNAs along with a potential activator for a plasma coagulation factor *in vivo*, to stimulate coagulation. As mentioned in Applicants response to the November 7, 2006, Office Action, the instant application describes the use of the claimed invention extracellularly, not intracellularly. Thus, no enablement is required to introduce the composition of the claimed invention into the cell. Moreover, techniques for introducing compositions extracellularly, specifically through the blood, are well-known. Thus, the claimed invention is enabled by the specification.

However, the Examiner has recommended amending the preamble to eliminate "pharmaceutical preparation" from the language of the claim, in order to overcome this rejection. Office action, pages 5-6. Solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, Applicants amend claim 1 to recite "[a] composition, which comprises a) an activator for plasma coagulation factor and b) an amount, sufficient for promoting coagulation, of natural or synthetic RNA, one or more coagulation-promoting fragments of natural or synthetic RNA, or peptide-nucleic acids" Applicants respectfully request that the instant rejection be withdrawn.

IV. The Claims Are Not Anticipated

A. Rejection over Shimkets and Braasch

The Examiner rejects claim 1 under 35 U.S.C. § 102(b) as allegedly being anticipated by Shimkets et al. (WO 00/58473) ("Shimkets") as evidenced by Braasch, for the reasons of record set forth in the November 7, 2005 Office Action. Office Action, page 6. Briefly, the Examiner alleged that Shimkets disclosed ORFX peptide nucleic acids (PNAs) that can hybridize to DNA or RNA, that the nucleic acids of the invention may enhance coagulation, that nucleic acid molecules of the invention can be incorporated into pharmaceutical compositions, and that PNAs in "high enough concentration would lead to toxicity, followed by cellular death and coagulation," as evidenced by Braasch. November 7, 2005 Office Action, page 8. Applicants respectfully traverse.

Applicants respectfully disagree with the Examiner's characterization of Shimkets. Shimkets discloses both polynucleotides and polypeptides related to the ORFXs. *See*, for example, Abstract. To distinguish between types of molecules (i.e. proteins, nucleic acids, PNAs, antibodies), Shimkets describes its ORFXs with a modifier, for example, an ORFX ***protein***, ORFX ***nucleic acid molecule***, ***PNAs*** of ORFX, or an anti-ORFX ***antibody***. See, for example, Specification at p. 26, lines 10-14 and p. 46, lines 4-7. Furthermore, in the only section discussing coagulation, Shimkets speculates that the "***protein*** of the invention . . . is expected to be useful in treatment of various coagulation disorders." Shimkets, Specification at p. 89, lines 20-26 (emphasis

added). Thus, Shimkets does not disclose that a nucleic acid or peptide-nucleic acid can enhance coagulation.

Moreover the Examiner states that "the PNA or antisense oligonucleotide taught by Shimkets et al. is considered to meet the instant limitation of an activator for plasma coagulation factor because the instant specification discloses that any RNA is a potential activator for a plasma coagulation factor." *Id.* Applicants respectfully disagree. Claim 1 requires two distinct elements, a) an activator for plasma coagulation factor and b) an amount of RNA, RNA fragments, or PNA. The specification makes it clear that these two elements are not the same. The specification clearly states that the RNA of the invention is a "cofactor" for an activator for plasma coagulation Specification, page 3, lines 23-25. The specification at no point describes or remotely suggests that RNA is an activator for a plasma coagulation factor. In fact, the specification further states that the composition comprising RNA or PNAs "***additionally*** includes an ***activator for a plasma coagulation factor***." *Id.* at page 3, lines 12-16 (emphasis added). The specification then defines various activators for a plasma coagulation factor including FSAP or its proenzyme, factor XII, kininogen, or prekallikrein. Id. at page 3, lines 17-19. Solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, Applicants have amended claim 3 and added claim 13 to further specify these activators. Thus, the language of the specification is unambigously distinguishing between RNAs and PNAs and activators for a plasma coagulation factor.

Furthermore, the Examiner relies on Braasch for the premise that PNAs in "high enough concentration would lead to toxicity, followed by cellular death and coagulation."

November 7, 2005 Office Action, page 8. However, in the section of Braasch discussing these non-selective toxicity and cell death effects, Braasch is discussing problems inherent in using antisense ***RNA*** that have been designed to function in the ***interior*** of the cell. *See* Braasch, p. 4503, col. 2, lines 7-11. Braasch was not discussing problems with PNAs or for that matter, RNAs on the cell exterior. *Id.* In fact, Braasch argues that PNAs may be a good alternative for use in an antisense-type capacity because their neutral backbone "prevents PNAs from binding to proteins that normally recognize polyanions, avoiding a major source of nonspecific interactions." Id. at p. 4507, col. 2, lines 47-51. Braasch is suggesting that PNAs are an alternative to RNA antisense molecules since they would be less prone to the major source of nonspecific interactions, likely reducing the toxicity and cell death consequences seen with the RNA. Further, Braasch is also silent on whether RNAs applied to the outside of a cell can lead to cell death and toxicity.

Since Shimkets nor Braasch teach or suggest the addition of an RNA or PNA ***and*** an activator for a plasma coagulation factor in a pharmaceutical preparation, Shimkets is missing a key limitation of the claims and cannot anticipate the instant application. Applicants respectfully request the withdrawal of this rejection.

B. Rejection over Moore and Braasch

The Examiner also rejects claim 1 under 35 U.S.C. § 102(b) as allegedly being anticipated by Moore et al. (U.S. Patent No. 6,248,724 B1) ("Moore") for the reasons of record set forth in the November 7, 2005 Office Action. Briefly, the Examiner suggests that Moore teaches antisense oligonucleotides and antisense PNAs, pharmaceutical

compositions comprising PNAs, and that that PNAs in "high enough concentration would lead to toxicity, followed by cellular death and coagulation," as evidenced by Braasch. November 7, 2005 Office Action, page 9. Applicants respectfully traverse.

Moore discloses "antisense oligonucleotide and antisense peptide nucleic acid compositions [that] specifically inhibit ACE gene expression." Moore, col. 2, line 66, to col. 3, line 2. However, Moore does not teach the application of these molecules with an activator for plasma coagulation. As stated above, the composition of claim 1 requires two distinct elements, a) an activator for plasma coagulation factor and b) an amount of RNA, RNA fragments, or PNA. The specification makes it clear that these two elements are not the same. The specification states that the RNA of the invention is a "cofactor" for an activator for plasma coagulation and that the composition comprising RNA or PNAs "***additionally*** includes an ***activator for a plasma coagulation factor***." Specification, page 3, lines 12-16 and 23-25 (emphasis added). The specification also defines various activators for a plasma coagulation factor including FSAP or its proenzyme, factor XII, kininogen, or prekallikrein. Id. at page 3, lines 17-19. Solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, Applicants have amended claim 3 and added claim 13 to further specify these activators. Since Moore does not teach the application of antisense oligonucleotides or PNAs ***and*** an activator for plasma coagulation, Moore is missing a key element of the claims and, consequently, cannot anticipate the instant application.

Furthermore, as also discussed in the arguments against Shimkets, Braasch was not discussing problems with PNAs or for that matter, RNAs on the cell exterior. *See* Braasch, p. 4503, col. 2, lines 7-11. Braasch suggested that PNAs are an alternative to RNA antisense molecules since they would be less prone to the major source of nonspecific interactions, likely reducing the toxicity and cell death consequences seen with the RNA. Further, Braasch was also silent on whether oligonucleotides applied to the outside of a cell can lead to cell death and toxicity.

For the aforementioned reasons, Applicants respectfully request that the rejections of claims 1 and 3 be withdrawn.

SUMMARY

In view of the above amendments and remarks, Applicants submit that this application is in condition for allowance. An early and favorable action is earnestly solicited.

Please grant any extensions of time required to enter this amendment and response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: Jared S. Cohen

Jared S. Cohen
Reg. No. 56,175
Phone: (202) 408-4026
Fax: (202) 408-4400
email: jared.cohen@finnegan.com